



# Investigating the patient with muscle weakness

An accurate diagnosis is crucial for the management of patients presenting with muscle disorders. There may be important medical consequences for the patients (such as cardiac, respiratory and anaesthetic complications) and genetic implications for both patients and their families.

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**Symptoms of muscle disorders**

Although muscle weakness can occur in both muscle and nerve disorders, this article focuses primarily on weakness as a manifestation of a muscle disorder. Patients with muscle disorders can present with various clinical symptoms including fatigue, muscle weakness and wasting, pain, and cramps and fasciculations.

Muscle weakness can be classified anatomically as follows:

- ocular (weakness of the eye muscles, causing double vision)
- facial (may cause difficulties with facial expressions and eating)
- bulbar (weakness of the muscles that control speech and swallowing)
- neck (weakness may produce head drop)
- truncal (can cause kyphosis and scoliosis)

- limb (affecting the upper or lower limbs).

Typically, muscle disorders tend to cause proximal weakness, but there are rare muscle conditions that can cause a distal pattern of weakness.

In the assessment of a patient with muscle weakness, the pattern of weakness will provide important clues to the underlying muscle disorder. Patients may have either a focal weakness, affecting only a few muscle groups, or generalised weakness, affecting many widespread muscle groups (Table 1). This article focuses mainly on adult patients presenting with chronic, generalised muscle weakness.

**Causes of generalised muscle weakness**

The causes of generalised muscle weakness may be classified as hereditary or acquired. It is useful also to consider the time course of the muscle weakness.

**IN SUMMARY**

- Patients with muscle disorders may present with various symptoms, including muscle weakness.
- Although muscle weakness often indicates a nerve or muscle condition, it can occur in association with systemic disorders such as endocrine disorders or electrolyte disturbance.
- An accurate diagnosis of muscle disorders is important as there may be genetic, medical and therapeutic implications.
- Important points to consider in the clinical history include the family history and a targeted history for specific symptoms and complications of muscle disorders.
- The creatine kinase (CK) level is a useful marker of muscle disease; however, a normal CK does not always exclude muscle disease.
- Other important tests that may be performed include electromyography and muscle MRI.
- Muscle biopsy is the gold standard investigation for muscle weakness.

Most muscle weaknesses are either subacute or chronic. Chronic weakness usually develops over months or years but may present more acutely. Acute weakness develops over hours, days or a couple of weeks. The causes of acquired generalised muscle weakness include: endocrine and metabolic disorders, medications (e.g. statins), toxins (e.g. alcohol and snakebite evenomation), inflammatory conditions, infectious agents and psychogenic causes (e.g. somatisation in depression). Important causes of acute muscle weakness and of subacute or chronic acquired muscle weakness are summarised in Tables 2 and 3. Table 4 lists the hereditary causes of muscle weakness.

### Diagnosis

An accurate diagnosis is especially important for the patient presenting with muscle weakness as there may be genetic, medical and therapeutic implications for the patient and his or her family.

### Genetic implications

The diagnosis of a hereditary muscle disorder may have significant consequences for the patient and his or her family. An accurate diagnosis means that the genetic counselling on the risks to future pregnancies can be more specific and accurate. In some congenital muscle disorders, such as myotonic dystrophy and congenital myasthenia gravis, the clinical

features may be much more severe in the neonate than in the parent. Occasionally, the parent is diagnosed after a diagnosis has been made in a neonate who presents with a more severe clinical phenotype.

### Medical complications

Some muscle disorders are associated with important medical consequences, such as cardiac, respiratory and anaesthetic complications. Patients who are aware of potential anaesthetic complications can wear a Medic Alert bracelet or advise the medical staff of medications that should be avoided. Those at risk of cardiac and respiratory problems will need to be monitored to detect these complications at an early stage. These associated medical issues may actually be the presenting feature of the underlying muscle disorder. For instance, cardiomyopathy in adulthood is occasionally seen as the presenting feature of some muscular dystrophies, including Becker muscular dystrophy.

### Treatment implications

Treatment options are available for some of the acquired muscle conditions, especially the inflammatory myopathies. Some of these treatments involve the use of potent immune-modifying medications that can have serious side effects. An accurate diagnosis is therefore critical to justify the use of such medications.

### Clinical assessment

The clinical assessment of patients with muscle weakness centres on the history and examination. Important points to elicit on the history include:

- the type of muscle symptoms, including their relation to exercise and the pattern of the weakness
- the time course for symptom onset
- medications used (past and present) and exposure to toxins (see Table 3)
- family history, which may provide clues to a hereditary muscle disorder, although many muscle conditions are sporadic or autosomal recessive.

**Table 1. Diagnostic features to consider in patients with muscle weakness**

#### Focal weakness

- Focal weakness may include weakness of individual muscles or muscle groups and may be asymmetrical. For example, weakness of the brachioradialis muscle occurs in facioscapulothoracic muscular dystrophy (FSH) and weakness of the finger flexors and quadriceps is seen in inclusion body myositis (IBM). Ptosis can be seen in mitochondrial disorders.
- Focal weakness can also occur as a presentation of a more generalised neuromuscular disorder. For instance, focal weakness can be seen in motor neurone disease (e.g. isolated foot drop or hand weakness) and distal myopathies.

#### Generalised weakness

- Generalised weakness typically has a proximal emphasis.
- It is important to exclude common medical causes (see Table 2), including medications and toxins, electrolyte disturbances and endocrine disorders.
- Additional clues to the diagnosis in a patient with generalised weakness may include:
  - ocular features: myasthenia, mitochondrial disorders
  - facial weakness: myotonic dystrophy, FSH
  - pharyngeal weakness: myasthenia, dermatomyositis, IBM
  - prominent hip or shoulder girdle weakness: limb-girdle muscular dystrophies or dystrophin-related muscular dystrophy
  - skin changes: connective tissue disorders and inflammatory myopathies, especially dermatomyositis.

#### Psychogenic weakness

- Consider psychogenic weakness if the patient does not fit into any other diagnostic group and investigations are normal.
- Clinical clues to psychogenic weakness include 'give-away' weakness (i.e. weakness out of proportion to the patient's disability or level of function) and generalised total body weakness.

Other features that may provide clues to the cause of muscle weakness include:

- the presence of typical rashes – e.g. periorbital rash, Gottron’s papules and nodules may give a clue to the diagnosis of dermatomyositis
- the presence of rhabdomyolysis, which occurs mainly in patients with metabolic disorders; patients may describe ‘Coca-Cola’ coloured urine
- myotonia, which may be described as stiffness and difficulty in relaxing the muscles (detected easily by asking patients to open and close their fists rapidly)
- cardiomyopathy and respiratory weakness
- anaesthetic complications.

Typically, patients with muscle disorders will have symmetrical and proximal weakness, and there may be wasting in the affected muscles. It is important to look for weakness in other areas that may be affected, including the eye, facial and bulbar muscles.

The sensory examination should be normal in patients with a muscle disorder, and the reflexes are usually normal, although they may be decreased if there is significant weakness. Reflexes are also reduced in patients with neuropathies presenting with proximal weakness, including Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP).

## Investigations

### Laboratory investigations

- **Measurement of serum enzyme levels.** Basic laboratory investigations for patients with muscle weakness include measurement of creatine kinase (CK). Other enzymes may be raised in association with CK, including lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Occasionally, elevation of the liver enzymes may indicate an underlying muscle disorder rather than an

## Table 2. Causes of acute generalised muscle weakness

### Electrolyte imbalance

Abnormalities in electrolyte levels, especially potassium, magnesium, calcium and phosphate, can lead to acute generalised muscle weakness.

### Rhabdomyolysis and myoglobinuria

Rhabdomyolysis and myoglobinuria may occur in individuals under the following conditions:

- severe electrolyte imbalance
- heatstroke
- after extreme amounts of exercise (e.g. after a marathon run)
- after excessive ingestion of alcohol (e.g. after an alcoholic binge)
- snakebite evenomation (in addition to myotoxic effects, there may be neurotoxic and haematologic effects).

Rhabdomyolysis and myoglobinuria may also occur in individuals with an underlying muscle disorder, including metabolic and hereditary muscle disorders.

### Periodic paralysis

Patients with periodic paralysis develop bouts of generalised muscle weakness in association with an acute electrolyte abnormality (e.g. hypokalaemic periodic paralysis). Periodic paralysis may be hereditary or acquired. Hereditary cases are usually associated with an abnormality in an electrolyte channel gene. Acquired cases are usually seen in association with thyrotoxicosis.

### Neuromuscular junction disorders

Myasthenia gravis can present acutely with generalised weakness. Botulism is an important, potentially fatal, condition to consider. It may occur in infants after the ingestion of botulinum toxin in honey.

### Guillain–Barré syndrome

Guillain–Barré syndrome is an acute nerve disorder characterised by ascending muscle weakness and sensory features. It may occur after an infection (e.g. upper respiratory tract infection or gastroenteritis) or vaccination. It may progress rapidly and patients may require ventilatory support.

underlying liver disease. The CK level can be a very sensitive but nonspecific marker of muscle disease. The yield of investigating for a muscle disorder increases with a higher CK level. In some muscle diseases, such as polymyositis, the CK level is a useful marker of disease activity. Exercise, recent minor muscle trauma (including recent intramuscular injection or electromyography) and viral illnesses can lead to mild elevations in CK level. Thus, if patients have a mildly elevated CK (i.e. up to three times the

upper limit of normal), it is useful to retest the CK at a later date when these factors are no longer an issue. A normal CK level does not, however, exclude a muscle disorder. Patients with weakness and a normal CK level should still be evaluated and considered for referral as conditions such as myasthenia and CIDP can be difficult to diagnose.

- **Measurement of electrolytes (including potassium, magnesium, calcium and phosphate).** Abnormal electrolyte levels may be a cause of the muscle weakness

continued

or provide a clue to the underlying disorder – e.g. low potassium levels may occur with diuretic use and in disorders such as Cushing’s disease.

- **Thyroid function tests.**
- **An autoimmune screen.** This is useful to look for the inflammatory myopathies and should include the erythrocyte sedimentation rate (ESR) and the antinuclear antibody (ANA) level. Measurement of the anti-double stranded DNA antibody (anti-dsDNA) is useful if systemic lupus erythematosus is suspected. Measurement of extractable nuclear antigens (ENAs) is useful in further classifying the inflammatory condition.

For instance, the anti-Jo1 antibody can be positive in polymyositis/ dermatomyositis. Measurement of angiotensin converting enzyme is useful if sarcoidosis is suspected.

- **Measurement of vitamin D level.** A normal vitamin D level is greater than 50 nmol/L, borderline levels are between 25 and 50 nmol/L, and muscle disorders occur when the level is below 25 nmol/L.
- **Measurement of lactate level.** A raised lactate level may be seen in patients with a mitochondrial disorder. Use of a tourniquet during venepuncture can lead to falsely elevated lactate levels.

### Neurophysiological investigations

Two important tests to consider in the evaluation of a patient with generalised muscle weakness are:

- the nerve conduction study (NCS) – to exclude neuropathy
- needle electromyography (EMG) – to detect the presence of a muscle disorder, provide information on disease activity and the muscles involved, and select an appropriate muscle for biopsy.

Further specialised neurophysiology techniques include repetitive nerve stimulation (RNS) and single fibre EMG (SFEMG) for the investigation of myasthenia gravis and other neuromuscular

**Table 3. Causes of chronic and subacute acquired generalised muscle weakness**

#### Endocrine

- Thyroid-related: both hyper- and hypothyroidism may cause muscle weakness.
- Parathyroid disorders (including hyperparathyroidism): may lead to muscle weakness, especially if the patient has associated osteomalacia.
- Vitamin D deficiency: muscle weakness can occur in people with very low vitamin D levels.
- Excess endogenous corticosteroids (Cushing’s disease).

#### Metabolic

Patients with metabolic muscle disorders may present with any of the following: asymptomatic elevation of the creatine kinase (CK) levels muscle pain or cramps, exercise intolerance, or muscle weakness.

The more common metabolic disorders to consider include:

- glucose and glycogen pathway disorders (e.g. McArdle’s disease)
- lipid metabolism disorders (an accumulation of fat droplets may be seen on the muscle biopsy)
- purine metabolism disorders (e.g. myoadenylate deaminase deficiency).

#### Medication-related

Many medications can cause muscle disorders, either by direct myotoxicity or indirectly through their actions on the body. Although such muscle disorders tend to be subacute or chronic, medications occasionally lead to acute muscle weakness. They may cause asymptomatic elevation of the CK level, myalgias, a frank myopathy

with muscle weakness or, occasionally, rhabdomyolysis. Medications that have been associated with muscle disorders include those listed below.

- Statins: all can lead to myopathy, but some are more likely to have this effect (e.g. cerivastatin was withdrawn from the market in 2001 due to its myotoxic effect). They are more likely to have myotoxic effects when used in higher doses or with other myotoxic agents.
- Other lipid-lowering medications, including gemfibrozil and ezetimibe: they are more likely to be associated with a muscle disorder when used with a statin.
- Corticosteroids, particularly fluorinated corticosteroids (muscle disorders are uncommon with low dose prednisolone use).
- Diuretics: may lead to electrolyte imbalance, especially of potassium and magnesium, resulting in muscle weakness.
- Colchicine: long term use for gout may be associated with a myopathy, especially in patients with coexisting renal impairment or when used with other potentially myotoxic agents such as cyclosporin.
- Some cardiac medications (e.g. amiodarone in high doses) may cause a myopathy.
- Isotretinoin: rarely associated with muscle weakness, but should be considered as it is often used in young patients to treat severe cystic acne.
- Chloroquine: high doses may cause a generalised myopathy.
- Emetine: present in ipecac syrup and used for the treatment of amoebic liver abscesses, it can lead to muscle weakness and cardiotoxicity.

transmission disorders. A neurologist normally requests these tests.

The flowchart on page 44 summarises an investigation pathway for patients presenting with muscle weakness.

### MRI

Increasingly, MRI is being used in the investigation of patients with muscle disorders. This investigation is normally requested by a neurologist or rheumatologist. The MRI is used to identify clinically affected muscles, including atrophic muscles or areas of significant myositis. This information may help in elucidating the cause of the disorder and deciding on a suitable muscle to biopsy.

### Other tests

Occasionally, other investigations are used to confirm the diagnosis of muscle disorders. For instance, if a mitochondrial disorder is suspected, the patient may be sent for tests involving the collection of blood, hair or urine for specialised mitochondrial DNA analyses. If sarcoidosis is considered, the patient may be sent for a chest x-ray, pulmonary CT scan or gallium scan to look for hilar lymphadenopathy or pulmonary fibrosis.

### Muscle biopsy

Muscle biopsy is the gold standard in the investigation of muscle weakness (Figures 1 and 2). It should be considered when-

ever there is any clinical suspicion of a muscle disorder, a very high CK level or abnormal EMG.

The selection of the muscle to be biopsied is an important decision. The muscle should be a clinically affected muscle. Muscles that are often biopsied include the quadriceps, the gastrocnemius and the deltoid muscle. Muscles that should be avoided are those that may lead to falsely abnormal results – e.g. those that have been recently subjected to trauma or used as the site for an intramuscular injection, including EMG.

There are two ways to perform a muscle biopsy. The open muscle biopsy is the standard method, requiring surgical

- Antiretroviral agents (e.g. zidovudine) can cause a myopathy. It must be noted that HIV infection/AIDS can be associated with a myopathy.
- Medications can exaggerate or cause a myasthenic state – e.g. penicillamine can cause a myasthenic-type state and aminoglycosides and neuromuscular blocking agents can exacerbate myasthenia gravis.

### Toxin-related

- Alcohol: muscle weakness may occur in people with chronic alcohol use or in those with a long history of frequent binge drinking (important to consider given the relatively high consumption of alcohol in Australia). Other neurological features that may occur with chronic alcohol use include neuropathies, cognitive impairment, unsteadiness from cerebellar dysfunction and seizures.

### Inflammatory

- Polymyositis and dermatomyositis: features that may point to an inflammatory myopathy are the typical rashes of dermatomyositis, including Gottron's papules and a 'heliotrope' rash. Patients with dermatomyositis are at an increased risk of having an underlying malignancy, thus investigations for malignancy should be considered.
- Inclusion body myositis (IBM): one of the more common inflammatory muscle disorders in people aged over 65 years, affecting more men than women, and sometimes misdiagnosed

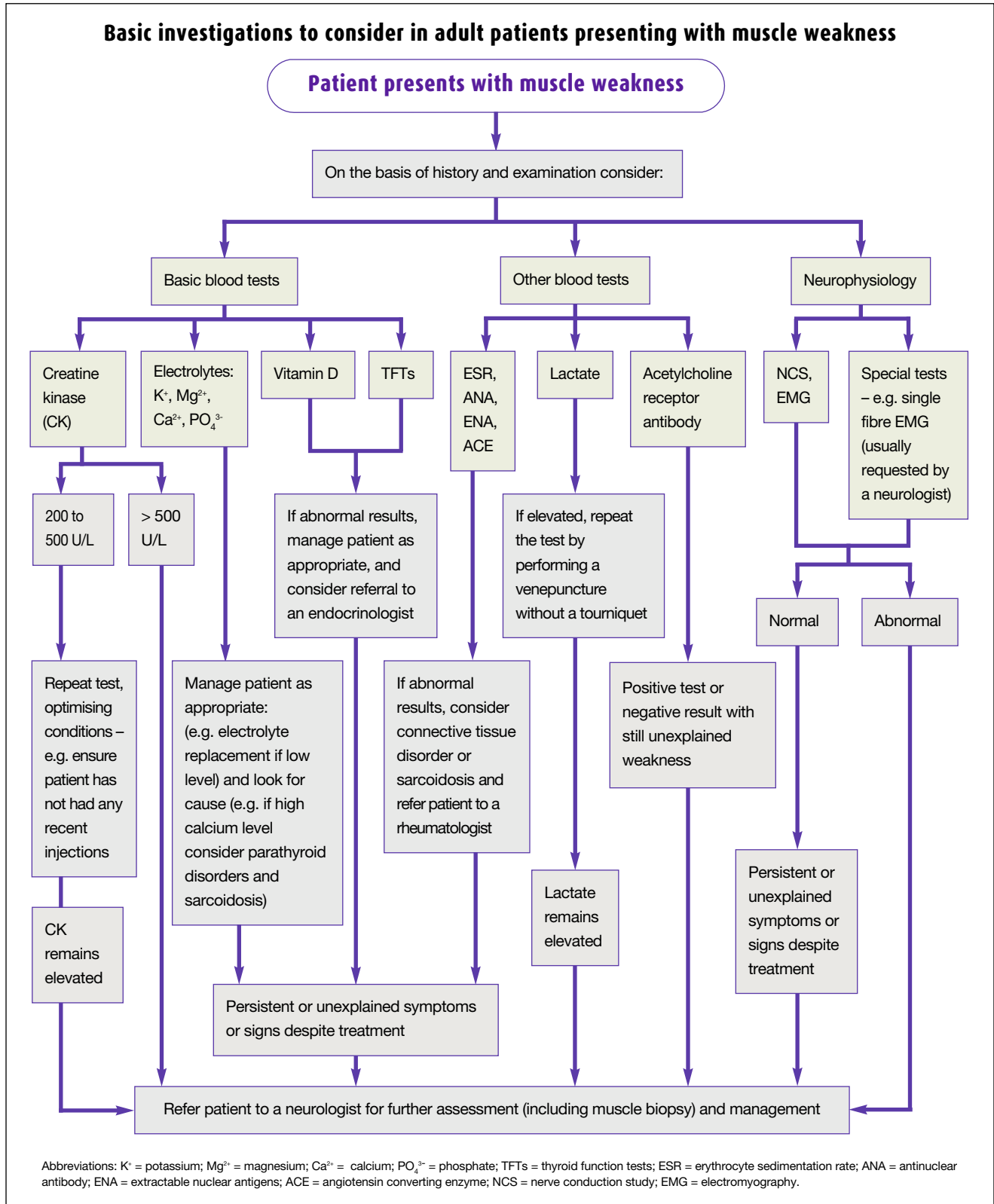
as polymyositis. Typically there is wrist and finger flexor weakness (e.g. problems gripping objects and doing up buttons) and quadriceps weakness. Difficulty with swallowing is also common. There are limited treatment options currently available for IBM.

- Sarcoidosis: myopathy is an uncommon feature of sarcoidosis. The more common clinical features are respiratory symptoms, inflammation and nodules in the lungs, and usually lymphadenopathy (e.g. in the hilum of the chest). Other manifestations include features of hypercalcaemia, joint inflammation and rashes.
- Connective tissue diseases (e.g. systemic lupus erythematosus and mixed connective tissue disease): may be associated with a myopathy. Features of a connective tissue disorder include arthropathy, rash and multisystem involvement.
- Polymyalgia rheumatica: a very common presentation in general practice. Patients have pain in the joints and periarticular tissues, especially around the limb girdle region. Typically the erythrocyte sedimentation rate is elevated.
- Chronic inflammatory demyelinating polyneuropathy: patients can present with mainly proximal weakness and, therefore, appear initially to have a muscle disorder. Typically, there is also distal weakness, hyporeflexia and sensory symptoms.

### Infectious

- Various infectious agents, especially the influenza virus, coxsackie viruses and Epstein Barr virus, may be myotoxic. Although a less common cause, HIV infection/AIDS can also cause a myopathy.

continued



### Table 4. Hereditary causes of muscle weakness

#### Muscular dystrophies

Important examples of the muscular dystrophies that may present in adulthood include:

- Myotonic dystrophy
- Facioscapulohumeral muscular dystrophy (FSH)
- Limb-girdle muscular dystrophy
- Becker muscular dystrophy.

#### Mitochondrial myopathies

Mitochondrial myopathies may be associated with ophthalmoplegia, migraines, neuropathy, strokes and seizures. Other non-neurological manifestations may include cardiac dysfunction and gastrointestinal symptoms. The serum and cerebrospinal fluid lactate levels tend to be elevated in patients with mitochondrial disorders.

#### Central core disease

Central core disease is a rare but important disorder to consider as affected patients are at high risk of malignant hyperthermia and anaesthetic complications. Patients may present with very minor features, such as an asymptomatic elevation of the creatine kinase level or a proximal myopathy.

excision of muscle tissue. The needle muscle biopsy, performed by a neurologist under local anaesthesia and light sedation, involves the extraction of cores of muscle tissue. The needle muscle biopsy can be used to obtain tissue for most diagnoses. The major exception is when an inflammatory myopathy is considered, in which case an open muscle biopsy is needed. The needle muscle biopsy may result in some twisting of the muscle fibres, preventing the identification of perifascicular atrophy that is important in the diagnosis of dermatomyositis.

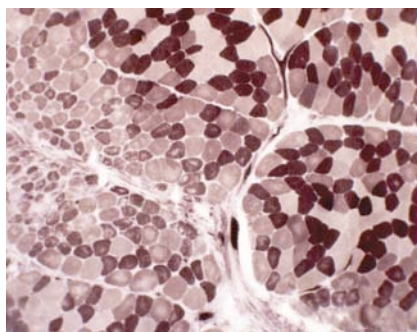


Figure 1. Muscle biopsy from a patient with polymyositis. Note the atrophy at the edge of the muscle fascicle.

Muscle tissue from a muscle biopsy is usually analysed by a neuropathologist. Occasionally, specific histopathological features will suggest a particular diagnosis. For instance, specific types of vacuoles are seen in colchicine myopathy and in inclusion body myositis. Further tests can be requested on the muscle biopsy tissue, including:

- specialised biochemical tests if a metabolic disorder is suspected
- immunohistochemistry or Western Blot analysis to analyse muscle proteins, which is particularly useful in the diagnosis of the muscular dystrophies.

#### Referral to a neurologist

Generally, all patients with muscle disorders should be referred to a neurologist at some point to aid in the further clinical assessment, diagnosis and management. This may include the selection of an appropriate muscle for biopsy, determined clinically and with the aid of EMG and MRI. To obtain an accurate diagnosis of polymyositis, a muscle biopsy should be performed before patients are commenced on corticosteroid therapy. In addition, the muscle pathology of many muscle conditions is quite subtle, and review of the muscle biopsy by a neurologist and neuropathologist may help in obtaining an accurate diagnosis. The neurologist will also decide on the need for further investigations, including mol-

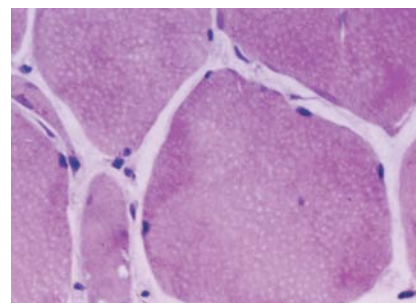


Figure 2. Muscle biopsy from a patient with inclusion body myositis. Note the typical inclusion bodies within the atrophic muscle fibres.

ecular assays such as the Western Blot, muscle biochemistry and genetic testing.

A referral to a neurologist is also made for the ongoing management of patients with muscle disorders, including the monitoring of hereditary muscle conditions and immunosuppression use in patients with inflammatory muscle disorders.

#### Conclusion

Weakness is a common presenting feature in patients with muscle disorders. Patients with muscle disorders may have cardiac, respiratory and anaesthetic complications. There may also be genetic implications following the diagnosis of a hereditary muscle disorder.

The causes of muscle weakness are diverse, reflected by the variety of investigations available to investigate patients with muscle weakness. The investigations chosen should be based on the clinical clues obtained and aimed at detecting the serious and treatable muscle conditions. **MT**

#### Further reading

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